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(54) Title: TOPICAL FORMULATIONS OF ACICLOVIR

(57) Abstract

An oil-in-water topical pharmaceutical formulation comprising aciclovir or a salt or an ester thereof, water and at least 10 % diethylene glycol monoethyl ether, and its use in the treatment or prevention of infections caused by Herpes zoster, Herpes varicella and Herpes simplex types 1 and 2.

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TOPICAL FORMULATIONS OF ACICLOVIR

This invention relates to a topical pharmaceutical formulation suitable for use in treating virus infections of the skin and mucosa, and in particular it relates to topical formulations containing 9-(2-hydroxyethoxymethyl)guanine, otherwise known as aciclovir, and hereinafter referred to as such.

Aciclovir and pharmaceutically acceptable salts and esters thereof are known to have antiviral activity against various classes of DNA and RNA viruses both *in vitro* and *in vivo*, see UK patent No. 1 523 865. In particular the compound is active against herpes simplex virus which causes herpetic keratitis in rabbits, herpetic encephalitis in mice, and cutaneous herpes in guinea pigs and mice. Aciclovir has been found to be effective in the treatment of herpes simplex virus and herpes zoster virus in humans.

Aciclovir suffers from the disadvantage that it has a low solubility in water and is almost totally insoluble in hydrophobic solvent systems. It is accordingly difficult to produce a topical formulation containing a sufficient dissolved concentration of active ingredient for it to exert its full effect and also to optimise the flux of the compound into the skin. In addition to ease of release it is also important that any formulation of a pharmaceutically active compound should be stable for long periods of time, should not lose its potency, should not discolour or form insoluble substances or complexes, and also should not be unduly irritating to the skin or mucosa.

European Patent No. 0 044 543 describes oil-in-water topical pharmaceutical formulations of aciclovir wherein the aqueous phase contains at least 30% of a water miscible polyhydric alcohol.

We have now found that oil-in-water topical pharmaceutical formulations of aciclovir comprising at least 10% by weight of diethylene glycol monoethyl ether have particularly advantageous properties. In particular, such formulations exhibit enhanced efficacy together with low irritancy and good physical stability.

The present invention accordingly provides a topical pharmaceutical formulation comprising water, aciclovir and at least 10% w/w of diethylene glycol monoethyl ether by weight of the formulation.

Preferably the formulation of the invention contains a maximum of 50% water.

Such a topical formulation may contain 0.075% to 10% w/w aciclovir or a salt or an ester thereof, from 10% to 50% w/w of diethylene glycol monoethyl ether, from 15% to 50% w/w water and an oil phase. Hereafter references to aciclovir should be understood to include also its pharmaceutically acceptable salts and esters unless the context clearly indicates otherwise.

In a preferred aspect the formulation comprises from 0.5% to 10% w/w aciclovir, from 20% to 40% w/w of diethylene glycol monoethyl ether, from 20% to 40% w/w water together with an oil phase, whilst the most preferred formulation comprises from 1% to 5% w/w aciclovir, from 30% to 40% w/w of diethylene glycol monoethyl ether, from 25% to 40% w/w water together with an oil phase.

Diethylene glycol monoethyl ether is manufactured by Gatttefossé S.A., 36 Chemin de Genas, b.p. 603, 69804 Saint-Priest Cedex, France, under the tradename TRANSCUTOL™.

The oil phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it is desirably comprised of a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, as explained in more detail below, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so called emulsifying ointment base which forms the oil dispersed phase of the emulsions.

Emulgents and emulsion stabilisers suitable for use in the formulation of the present invention include cetyl alcohol, sodium lauryl sulphate, stearyl alcohol

and polyoxyethylene alkyl ethers, such as brij 721 and brij 72 and polyoxyl stearyl ethers, for example steareth 2 and steareth 21.

The formulations of the invention may also comprise additional components in the aqueous phase, for example polyhydric alcohols such as propylene glycol. Preferably the formulations of the invention comprise from 0 to 30% by weight of propylene glycol.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of aciclovir in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dialkyl esters such as diisopropyl adipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a mixed ester of 2-ethyl hexanoic acid with a blend of cetyl or stearyl alcohols known as Crodamol CAP may be used, the last three being the preferred esters. These may be used singly or incombination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

A preferred formulation according to the invention comprises diethylene glycol monoethyl ether, 30-40% w/w; aciclovir, approximately 5% w/w; cetyl alcohol 3-10% w/w; stearyl alcohol, 4-10% w/w; propylene glycol, 0-10% w/w; light mineral oil, 8-15% w/w; steareth 21 or brij 721, 2-5% w/w; steareth 2 or brij 72, 1-3% w/w; and purified water to 100% w/w.

The formulations of the invention may, if desired, include one or more pharmaceutically acceptable preservatives. However, we have found that the use of preservatives is not essential in the formulations of the invention, which finding represents an advantage of the said formulations.

The present invention further provides a method for the preparation of a topical pharmaceutical formulation, as hereinbefore defined, which comprises mixing

the combination of aciclovir, diethylene glycol monoethyl ether and water with the oil phase.

The manner of formulating the emulsion will of course vary according to the amount and nature of the constituents, but nevertheless follows known techniques in emulsion technology (see the Pharmaceutical Codex, London, the Pharmaceutical Press, 1979). For example the aciclovir may be initially incorporated wholely in the aqueous portion where it may form a solution alone, or a mixed solution/suspension, and then emulsified with the ointment base. Alternatively where high concentrations of aciclovir are being used, a part of the aqueous portion may be formulated as an emulsion, and the balance of the water, diethylene glycol monoethyl ether and aciclovir added to and dispersed into the emulsion. In another technique the aciclovir may be included in the emulsifying ointment prior to emulsification with the aqueous portion. In using these procedures, it is preferable to heat the aqueous portion and the ointment base to about 40 to 80°C, preferably 50 to 70°C, prior to emulsification which may be achieved by vigorous agitation using for example a standard laboratory mixer. Finer dispersions of the oil phase may be obtained by homogenising or milling in a colloidal mill.

A topical formulation of the present invention may be used in the treatment or prevention of viral infections caused for example by Herpes zoster, Herpes varicella and Herpes simplex types I and 2, which cause diseases such as shingles, chicken pox, cold sores and genital herpes. The formulation should desirably be applied to the affected area of skin from 1 to 6 times daily, preferably from 3 to 5 times.

The following examples illustrate the invention and are not intended as a limitation thereof.

Example 1

Ingredient	% w/w
TRANSCUTOL™	40.0
aciclovir	5.0
stearyl alcohol	5.0
cetyl alcohol	4.0
light mineral oil	10.2
brij 721	2.5
brij 72	2.3
Purified water	to 100

The oil phase comprising stearyl alcohol, cetyl alcohol, light mineral oil, brij 72 and brij 721 is heated to 70-75°C with mixing. Purified water is heated to 65-70°C and added to the oil phase, maintaining the temperature at 70-75°C, with mixing to form an emulsion. The mixture is maintained at a temperature of 70-75°C for approximately 5 minutes. TRANSCUTOL™ is weighed into an appropriate container and aciclovir added with mixing to form a suspension. The aciclovir suspension is added to the emulsion, rinsing in with a small amount of purified water. The emulsion is homogenized for approximately 5 minutes, then made up to final batch weight with purified water. The resulting cream is cooled to ambient temperature (approximately 30°C) with continuous mixing and filled into suitable tubes which are then sealed.

Example 2

Ingredient	% w/w
TRANSCUTOL™	30.0
aciclovir	5.0
stearyl alcohol	5.0
cetyl alcohol	4.0
light mineral oil	10.2
brij 721	2.5
brij 72	2.3
propylene glycol	10.0
Purified water	to 100

The oil phase comprising stearyl alcohol, cetyl alcohol, light mineral oil, brij 72 and brij 721 is heated to 70-75°C with mixing. Purified water is heated to 70-75°C and added to the oil phase, maintaining the temperature at 70-75°C, with mixing to form an emulsion. The mixture is maintained at a temperature of 70-75°C for approximately 5 minutes. TRANSCUTOL™ is weighed into an appropriate container and propylene glycol and aciclovir added with mixing to form a suspension which is homogenized at 65-70°C for approximately 5 minutes. The propylene aciclovir suspension is added to the emulsion at 50-70°C, suitably 50-55°C, rinsing in with a small amount of purified water. The emulsion is homogenized for approximately 5 minutes, then made up to final batch weight with purified water. The resulting cream is cooled to ambient temperature (approximately 30°C) with continuous mixing and filled into suitable tubes which are then sealed.

Example 3

The formulations described in Examples 1 and 2 may alternatively be prepared by the following modified procedure.

The oil phase is weighed and heated to 70-75°C with continuous slow mixing. Purified water is heated to 65-70°C. The purified water is added with propeller agitation to the suspension of aciclovir in TRANSCUTOL™. The resulting aqueous mixture is heated to 65-70°C. Whilst maintaining the temperature of the oil phase at 70-75°C, the aqueous phase is slowly added with sweep agitation for at least 5 minutes. The aqueous phase container is rinsed with purified water and the rinsings added to the main batch. The temperature of the batch is maintained at 70-75°C and the batch is homogenized for at least 5 minutes. The batch is cooled to 30-35°C with continuous sweep agitation and purified water added to adjust to final batch weight. The batch is mixed until uniform and cooled to 30°C.

Example 4 Experimental Data

Herpes Simplex Virus Animal Data: Mouse Snout Model

METHODS: Female HRS/J mice were infected cutaneously with wild-type HSV-1. After the mice were anaesthetised with ketamine and xylazine, the skin of the snout region was lightly abraded with a Dremel® roto-tool. Groups of ten mice were then innoculated on the skin of the snout from an SC-16 HSV stock solution diluted to a final concentration of 1 E6 PFU/ml. The abrasion area was then swabbed for ten seconds with a sterile cotton swab soaked with the viral stock.

TREATMENT: Mice were treated for five days starting three days post-innoculation (PI) and continues through day eight. Mice were treated topically twice daily at 0800 and 1400 hours.

TREATMENT GROUPS:
1. No treatment (N=15)
2. 5% Aciclovir in formulation A (N = 30)
3. 5% Aciclovir in formulation B (N = 30)

OUTCOME ASSESSMENT: Lesions were scored at the same time each day. During dosing period lesion scores were assessed prior to the first treatment application in the morning. The scoring system is outlined below:

0 = Normal skin
+1 = 1 to 5 discrete lesions
+2 = $\geq$ 6 discrete lesions
+3 = confluent lesions
+4 = necrotic lesions or death

STATISTICAL ANALYSIS: The lesions are graphed and the average area under the curve (AUC) is calculated to compare compound efficacies. Statistical analysis of data is performed using the unpaired t-test assuming equal variances (Microsoft® Excel program, version 4.0).

Formulation A: 5% w/w aciclovir
40% diethylene glycol monoethyl ether
4% cetyl alcohol
5% stearyl alcohol
10.2% light mineral oil
2.3% brij 72
2.5% brij 721
31% water

Formulation B: 5% w/w aciclovir
30% diethylene glycol monoethyl ether
10% propylene glycol
4% cetyl alcohol
5% stearyl alcohol
10.2% light mineral oil
2.3% brij 72
2.5% brij 721
31% water

Results

Treatment Group	Day PI/Average Lesion Score 1	2	3	4	5	6	7	8	Area Under the Curve (AUC)
1	0.0	0.0	0.0	0.1	2.1	3.3	3.9	4.0	11.4
2	0.0	0.0	0.1	0.1	0.3	0.9	1.5	2.0	3.9
3	0.0	0.0	0.0	0.1	0.9	1.5	2.7	3.2	6.8

Pairwise Treatment Comparisons	t-Value[1] ($P < 0.05$)
No treatment 1 vs. treatment 2	***
No treatment 1 vs. treatment 3	***
Treatment 2 vs. treatment 3	***

[1] Alpha = 0.05, Confidence 0.05, Critical Value of T = 2.706

*** - Statistically significant difference between paired treatments

Claims

1. A topical pharmaceutical formulation comprising water, aciclovir or a pharmaceutically acceptable salt or ester thereof and at least 10% w/w diethylene glycol monoethyl ether.

2. A formulation as claimed in claim 1 comprising 0.075% to 10% w/w aciclovir or a pharmaceutically acceptable salt or ester thereof, 10% to 50% w/w of diethylene glycol monoethyl ether, from 15% to 50% w/w water and an oil phase.

3. A formulation as claimed in claim 1 comprising 0.5% to 10% w/w aciclovir or a pharmaceutically acceptable salt or ester thereof, 20% to 40% w/w of diethylene glycol monoethyl ether, 20% to 40% w/w water together with an oil phase.

4. A formulation as claimed in claim 1 comprising 1% to 5% aciclovir or a pharmaceutically acceptable salt or ester thereof, 30% to 40% w/w diethylene glycol monoethyl ether, 25% to 40% w/w water together with an oil phase.

5. A formulation as claimed in any of claims 2 to 4, wherein the oil phase comprises at least one hydrophilic emulsifier and at least one lipophilic emulsifier, together with at least one fat and/or oil.

6. A formulation as claimed in any preceding claim, which contains at least one emulsifier selected from cetyl alcohol, sodium lauryl sulphate, stearyl alcohol and a polyoxyethylene alkyl ether.

7. A formulation as claimed in any preceding claim, further comprising at least one polyhydric alcohol in the aqueous phase.

8. A formulation as claimed in claim 1 which comprises 30-40% w/w diethylene glycol monoethyl ether, approximately 5% w/w aciclovir, 3-10% w/w cetyl alcohol, 4-10% w/w stearyl alcohol, 0-10% w/w propylene glycol, 8-15% w/w light mineral oil, 2-5% w/w steareth 21 or brij 721, 1-3% w/w steareth 2 or brij 72, and purified water to 100% w/w.

9. A process for the preparation of a topical pharmaceutical formulation as claimed in any of the preceding claims comprising mixing the combination of aciclovir or a pharmaceutically acceptable salt or ester thereof, diethylene glycol monoethyl ether and water with the oil phase.

10. A method of treatment and/or prevention of infections in humans or animals caused by Herpes zoster, Herpes varicella and Herpes simplex types 1 and 2 comprising administering to the subject an effective amount of a formulation as claimed in any of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 15614 A (AGIS IND 1983 LIMITED ;GODWIN EDGAR JAMES (GB)) 21 July 1994 see page 7 ---	1
Y	EP 0 044 543 A (WELLCOME FOUND) 27 January 1982 cited in the application see page 2, line 8 - line 21; claims 1-12 ---	1-10
Y	WO 95 35095 A (YISSUM RES DEV CO ;TOUITOU ELKA (IL)) 28 December 1995 see page 12; example VII see claims 1-9 ---	1-10
Y	WO 90 11064 A (CYGNUS RESEARCH CORP) 4 October 1990 see page 3, line 5 - line 6 ---	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 015, no. 231 (C-0840), 12 June 1991 & JP 03 072426 A (TEIKOKU SEIYAKU KK), 27 March 1991, see abstract -----	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..ional Application No
PCT/GB 97/00779

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9415614 A	21-07-94	IL 104283 A	05-12-96
		AU 671704 B	05-09-96
		AU 5711894 A	15-08-94
		CA 2152907 A	21-07-94
		EP 0677126 A	18-10-95
		JP 8505850 T	25-06-96
		US 5585379 A	17-12-96
EP 0044543 A	27-01-82	GB 2080106 A,B	03-02-82
		AR 225680 A	15-04-82
		AU 547391 B	17-10-85
		AU 7307381 A	21-01-82
		BG 60450 B	28-04-95
		CA 1172169 A	07-08-84
		CY 1309 A	06-12-85
		HK 95485 A	06-12-85
		JP 1048885 B	20-10-89
		JP 1563405 C	12-06-90
		JP 57042615 A	10-03-82
		KE 3561 A	01-11-85
		SU 1375113 A	15-02-88
		US 4963555 A	16-10-90
WO 9535095 A	28-12-95	US 5540934 A	30-07-96
		AU 2977695 A	15-01-96
WO 9011064 A	04-10-90	US 4973468 A	27-11-90
		AU 629331 B	01-10-92
		AU 5417490 A	22-10-90
		CA 2012875 A,C	22-09-90
		EP 0464150 A	08-01-92
		JP 2550441 B	06-11-96
		JP 4505157 T	10-09-92
		KR 9510324 B	14-09-95
		US 5053227 A	01-10-91
		US 5059426 A	22-10-91